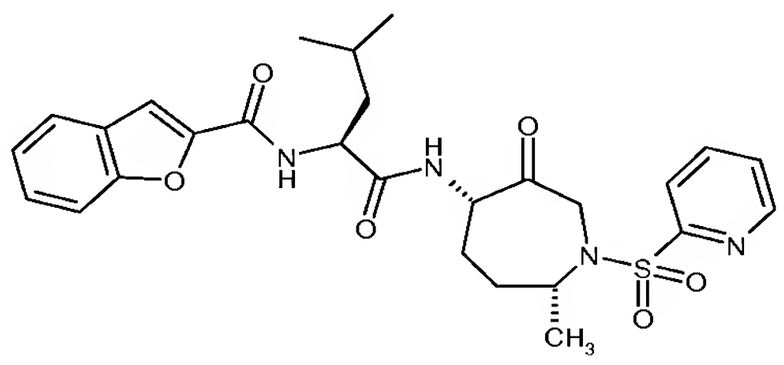
Amendments to the claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. (Original) A method of preparing benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide, of Formula I:

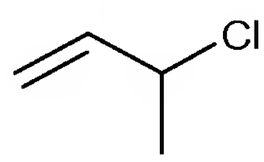


I

comprising the steps of:

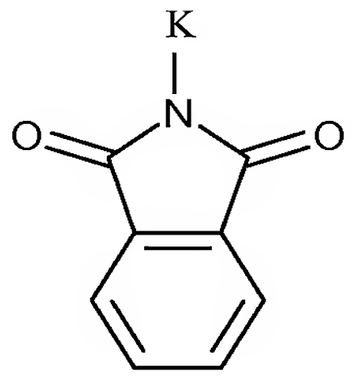
A. preparation of a sulfonamide fragment, further comprising the steps of:

Step 1. reacting 3-chloro-1-butene 1-1:

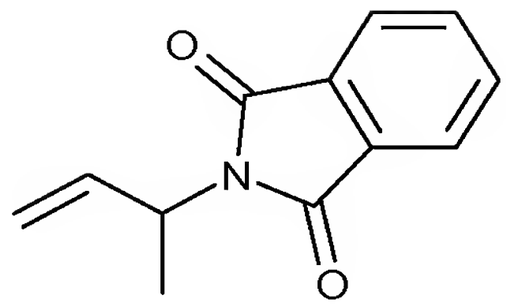


1-1

with potassium phthalimide:



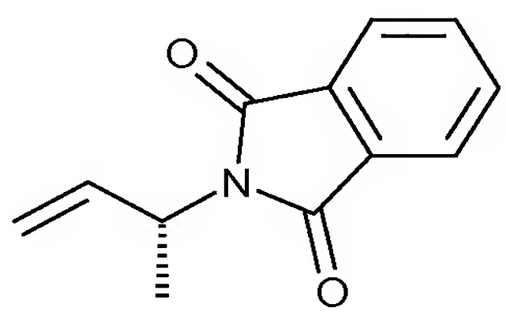
in the presence of an alkali metal carbonate base to form a compound 1-2, N-(α-methylallyl) phthalimide, as a racemate;



;

1-2

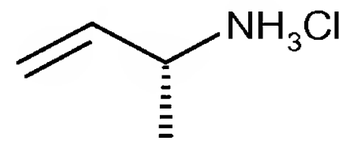
Step 2. chiral chromatography of the racemic compound 1-2 to provide the (R)-enantiomer 1-3;



.

1-3

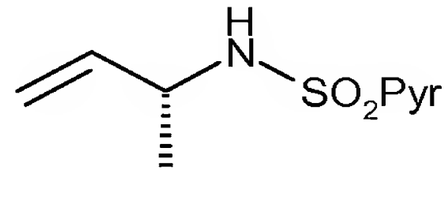
Step 3. reacting the compound 1-3 with a first amine-substituted compound selected from the group consisting of: C_{1-6} alkylamine, C_{2-6} alklanolamine, and C_{2-6} alkyldiamine in an alcoholic solvent to form a reaction product, 2-amino-3-butene, and then purifying the reaction product by azeotropic distillation with ethanol, and then further treating the purified reaction product with gaseous HCl to provide the amine hydrochloride 1-4, 2-amino-3-butene hydrochloride



;

1-4

Step 4. Coupling 2-chlorosulfonyl pyridine with the amine hydrochloride 1-4 to form the pyridine sulfonamide fragment 1-5, (R)-2-pyridinesulfonyl-N-(α-methylallyl) amine

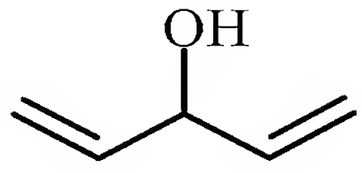


;

1-5

B. preparation of an epoxide fragment, further comprising the steps of:

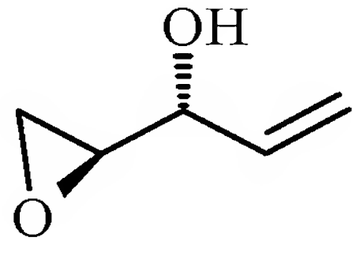
Step 1B. epoxidation of 1,4-pentadien-3-ol 2-1



;

2-1

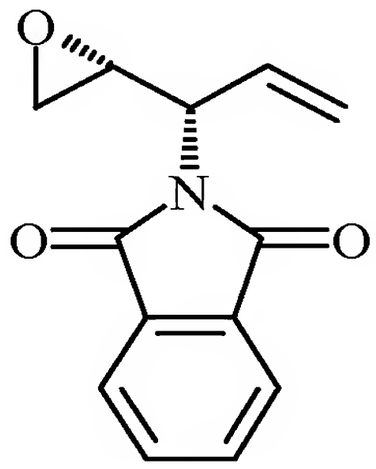
to provide (2S,3R)-1,2-epoxy-4-penten-3-ol 2-2



;

2-2

Step 2B. Mitsunobu reaction of (2S,3R)-1,2-epoxy-4-penten-3-ol 2-2 to form the nitrogen protected epoxide fragment 2-3, 2-[(1S)-1-(2R)-oxiranyl-2-propenyl]-1H-isoindole-1,3(2H)-dione

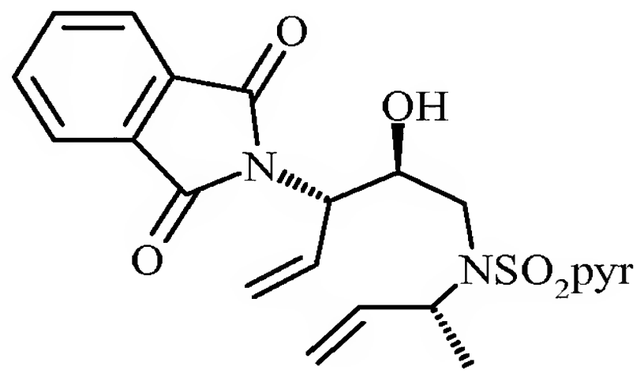


;

2-3

C. coupling of the the sulfonamide fragment and the epoxide fragment to provide the compound of Formula I, further comprising the steps of:

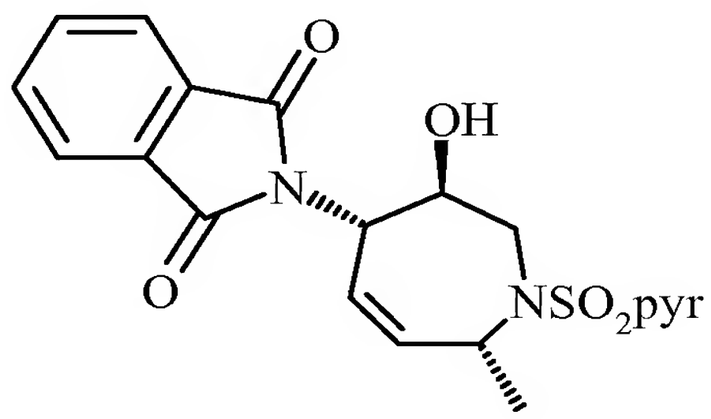
Step 5. addition of the sulfonamide fragment 1-5 and the epoxide fragment 2-3 to provide *N*-(2S,3S)-3-[(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)-2-hydroxy-4-pentenyl]-*N*-[(1*R*)-1-methyl-2-propenyl]-2-pyridinesulfonamide 3-1



;

3-1

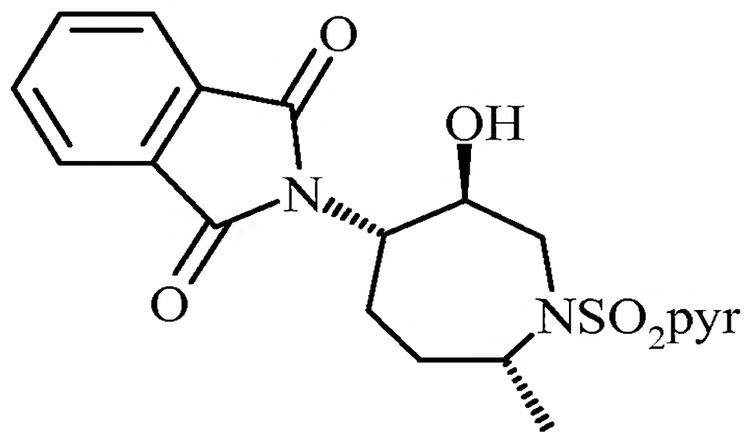
Step 6. reaction of the compound 3-1 with a transition metal alkylidene catalyst to provide compound 3-2, (3*S*,4*S*,7*R*)-4-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)-2,3,4,7-tetrahydro-7-methyl-1-(2-pyridinylsulfonyl)-1*H*-azepin-3-ol



;

3-2

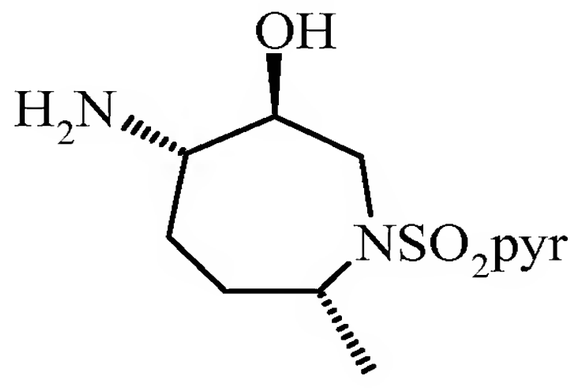
Step 7. hydrogenation of the compound 3-2 to provide the dihydro compound 3-3, (3*S*,4*S*,7*R*)-4-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)-2,3,4,5,6,7-hexahydro-7-methyl-1-(2-pyridinylsulfonyl)-1*H*-azepin-3-ol



;

3-3

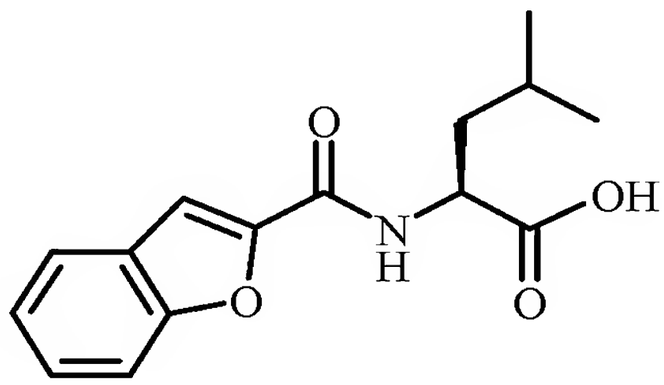
Step 8. deprotection of the azepanone 4-amino function of the compound 3-3 to provide the amino alcohol compound 3-4, (3*S*,4*S*,7*R*)-4-amino-2,3,4,5,6,7-hexahydro-7-methyl-(2-pyridinylsulfonyl)-1*H*-azepin-3-ol



;

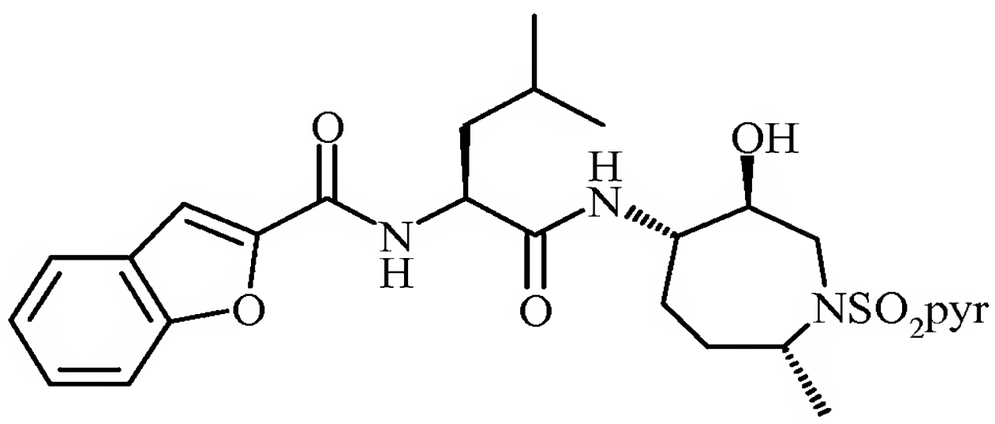
3-4

Step 9A. coupling of the amino alcohol 3-4 with the side chain carboxylic acid 3-5, (2*S*)-2-[(2-benzofuranylcarbonyl)amino]-4-methylpentanoic acid



3-5

to provide the azepine alcohol 3-6, {(S)-1-[(3S,4S,7R)-3-hydroxy-7-methyl-1-1(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

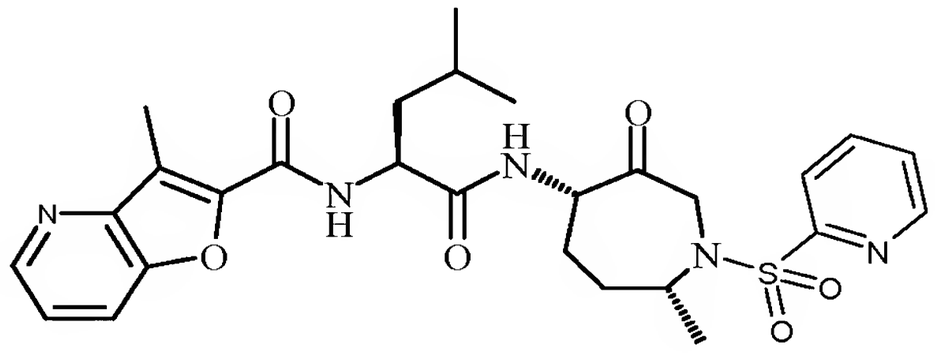


3-6

and

Step 10A. oxidation of amino alcohol 3-6 to provide the compound of Formula I.

2. (Original) A method of preparing 3-methyl-N-[(1S)-3-methyl-1-({[(4S,7R)-7-methyl-3-oxo-1-(2-pyridinylsulfonyl) hexahydro-1H-azepin-4-yl]amino}carbonyl)butyl]furo[3,2-b]pyridine-2-carboxamide

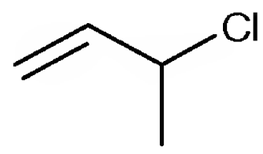


II

comprising the steps of:

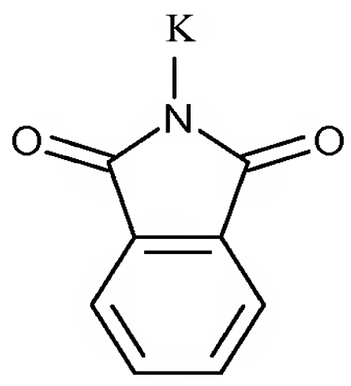
A. preparation of a sulfonamide fragment, further comprising the steps of:

Step 1. reacting 3-chloro-1-butene <u>1-1</u>:

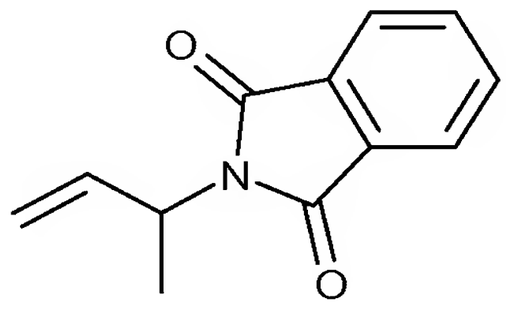


1-1

with potassium phthalimide:



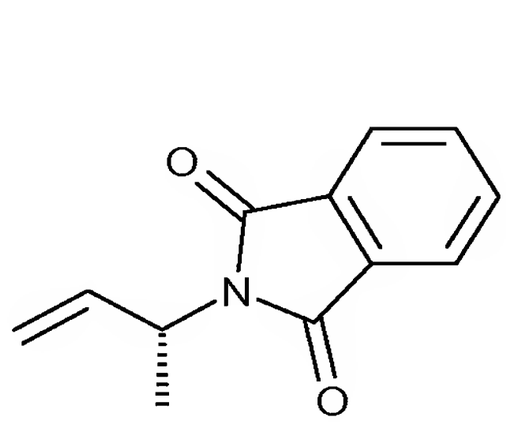
in the presence of an alkali metal carbonate base to form a compound <u>1-2</u>, N-(α-methylallyl) phthalimide, as a racemate;



;

1-2

Step 2. chiral chromatography of the racemic compound <u>1-2</u> to provide the (R)-enantiomer <u>1-3</u>;

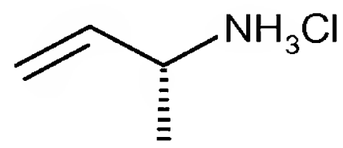


;

1-3

Step 3. reacting the compound <u>1-3</u> with a first amine-substituted compound selected from the group consisting of: C_{1-6} alkylamine, C_{2-6} alklanolamine, and C_{2-6} alkyldiamine in an alcoholic solvent to form a reaction product, 2-amino-3-butene, and then purifying the reaction product by azeotropic distillation with ethanol, and

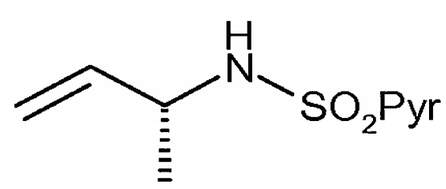
then further treating the purified reaction product with gaseous HCl to provide the amine hydrochloride 1-4, 2-amino-3-butene hydrochloride



;

1-4

Step 4. Coupling 2-chlorosulfonyl pyridine with the amine hydrochloride 1-4 to form the pyridine sulfonamide fragment 1-5, (R)-2-pyridinesulfonyl-N-(α-methylallyl) amine

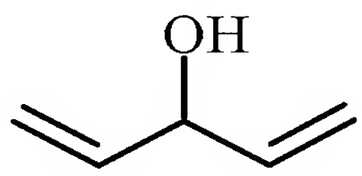


;

1-5

B. preparation of an epoxide fragment, further comprising the steps of:

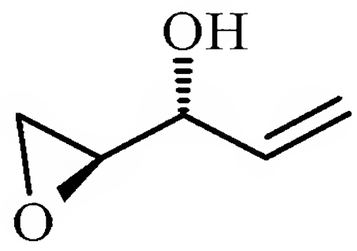
Step 1B. epoxidation of 1,4-pentadien-3-ol 2-1



;

2-1

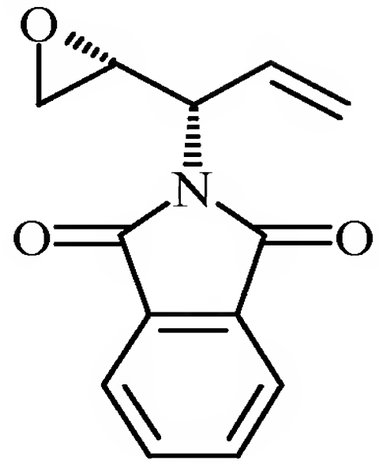
to provide (2S,3R)-1,2-epoxy-4-penten-3-ol 2-2



;

2-2

Step 2B. Mitsunobu reaction of (2S,3R)-1,2-epoxy-4-penten-3-ol 2-2 to form the nitrogen protected epoxide fragment 2-3, 2-[(1S)-1-(2R)-oxiranyl-2-propenyl]-1H-isoindole-1,3(2H)-dione

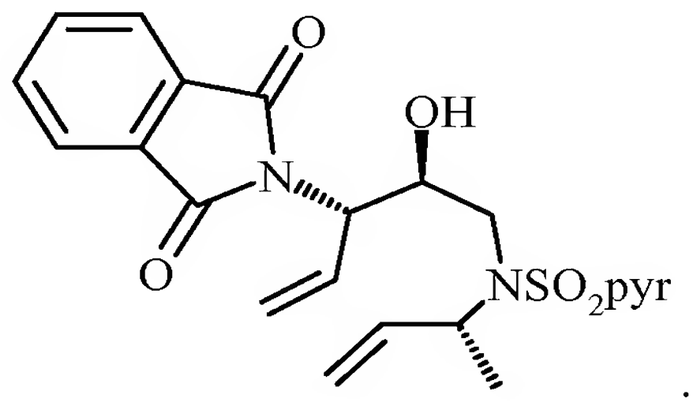


;

2-3

C. coupling of the the sulfonamide fragment and the epoxide fragment to provide the compound of Formula I, further comprising the steps of:

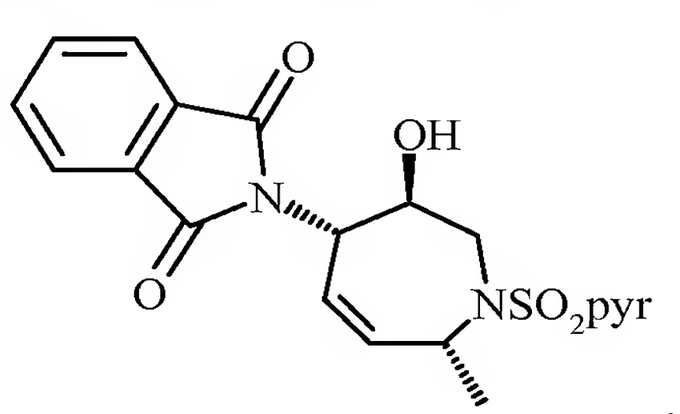
Step 5. addition of the sulfonamide fragment 1-5 and the epoxide fragment 2-3 to provide *N*-(2S,3S)-3-[(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)-2-hydroxy-4-pentenyl]-*N*-[(1*R*)-1-methyl-2-propenyl]-2-pyridinesulfonamide 3-1



;

3-1

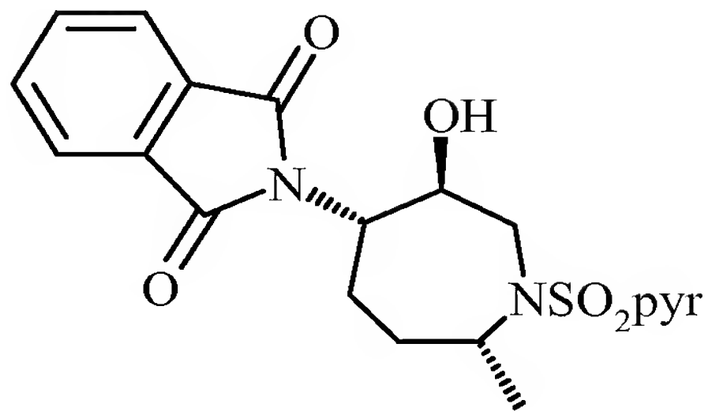
Step 6. reaction of the compound 3-1 with a transition metal alkylidene catalyst to provide compound 3-2, (3*S*,4*S*,7*R*)-4-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)-2,3,4,7-tetrahydro-7-methyl-1-(2-pyridinylsulfonyl)-1*H*-azepin-3-ol



;

3-2

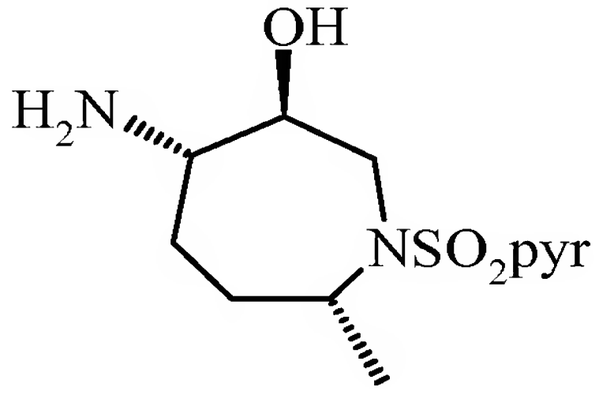
Step 7. hydrogenation of the compound 3-2 to provide the dihydro compound 3-3, (3*S*,4*S*,7*R*)-4-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)-2,3,4,5,6,7-hexahydro-7-methyl-1-(2-pyridinylsulfonyl)-1*H*-azepin-3-ol



;

3-3

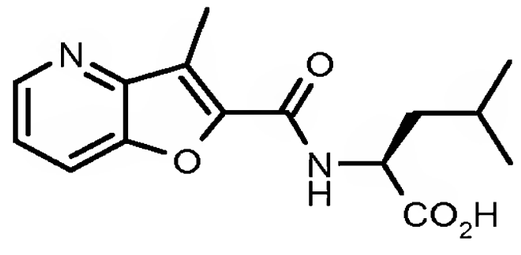
Step 8. deprotection of the azepanone 4-amino function of the compound 3-3 to provide the amino alcohol compound 3-4, (3*S*,4*S*,7*R*)-4-amino-2,3,4,5,6,7-hexahydro-7-methyl-(2-pyridinylsulfonyl)-1*H*-azepin-3-ol



;

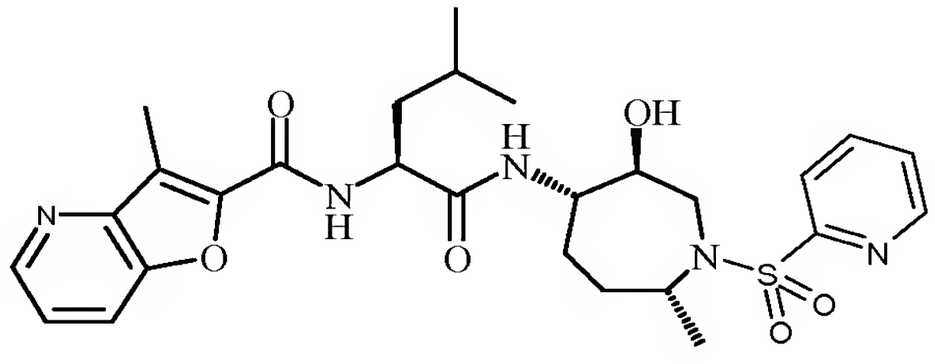
3-4

Step 9B. coupling of the amino alcohol 3-4 with the side chain carboxylic acid 6-3, N-[(3-methylfuro[3,2-b]pyridine-2-yl)carbonyl]-L-leucine



6-3

to provide the azepine alcohol 5-1, N-[(1S)-1-({[(3S,4S,7R)-3-hydroxy-7-methyl-1-(2-pyridinylsulfonyl)hexahydro-1H-azepin-4-yl]amino}carbonyl)-3-methylbutyl]-3-methylfuro[3,2-b]pyridine-2-carboxamide



and:

Step 10. Oxidation of amino alcohol 5-1 to provide the compound of Formula II.

3. (Currently Amended) A method according to ~~Claims 1 or 2~~Claim 1 wherein in Step 1 the alkali metal carbonate base is selected from the group consisting of: sodium carbonate, lithium carbonate, and potassium carbonate and the reaction is carried out in an aprotic polar solvent.

4. (Original) A method according to Claim 3 wherein the alkali metal carbonate base is potassium carbonate and the aprotic polar solvent is N,N-dimethylformamide which is heated at 135 ^{o}C .

5. (Currently Amended) A method according to ~~Claims 1 or 2~~Claim 1 wherein in Step 2 the chiral chromatography is multiple column chromatography where in MCC is used as part of a two-stage "enriching-polishing" procedure wherein in the first stage, a first pass is made using SMB chromatography for enrichment, followed by a second stage wherein a second pass using a second separation technique selected from the group consisting of: MCC, HPLC and crystallization to enhance the enrichment is made.

6. (Original) A method according to Claim 5 wherein compound 1-3 is provided in 80-100% enantiomeric excess.

7. (Original) A method according to Claim 5 wherein compound 1-3 is provided in at least 90% enantiomeric excess.

8. (Original) A method according to Claim 5 wherein the second separation technique is multiple column chromatography.

9. (Original) A method according to Claim 5 wherein the chiral stationary phase is selected from the group consisting of: CHIRALPAK AD, CHIRALCEL OJ, CHIRALCEL OD-H, WHELK-O 1, Kromasil DNB and Kromasil TTB.

10. (Original) A method according to Claim 9 wherein the chiral stationary phase is CHIRALPAK AD.

11. (Original) A method according to Claim 5 wherein the mobile phase is a single component or a mixture selected from the group consisting of: hexane and heptane, methanol, ethanol and 2-propanol, MTBE, ethyl acetate, acetone, and acetonitrile.

12. (Currently Amended) A method according to ~~Claims 1 or 2~~Claim 1 wherein in Step 3, the C_{2-6} alkanolamine is ethanolamine , the C_{2-6} alkyldiamine is 1,2-diaminoethane , and the C_{1-6} alkylamine is aminomethane, and the alcoholic solvent is ethanol.

13. (Currently Amended) A method according to ~~Claims 1 or 2~~Claim 1 wherein Step 4 is conducted in an aprotic solvent in the presence of an amine base, wherein the aprotic solvent is selected from the group consisting of: toluene, tetrahydrofuran, ethyl acetate, and methylene chloride and the amine base is selected from the group consisting of: triethylamine, i-Pr_2EtN, and *N*-methylmorpholine.

14. (Original) A method according to Claim 13 wherein the aprotic solvent is methylene chloride and the amine base is triethylamine.

15. (Currently Amended) A method according to ~~Claims 1 or 2~~Claim 1 wherein in Step 1B, the epoxidation is conducted in the presence of a peroxide selected from the group consisting of: cumene hydroperoxide and *tert*-butylhydroperoxide, with $Ti(O\textit{i}Pr)_4$ and (-)-diisopropyl tartrate ((-)-DIPT) in catalytic or stoichiometric amounts over 4Å molecular sieves in methylene chloride at –30°C.

16. (Original) A method according to Claim 15 wherein the peroxide is cumene hydroperoxide.

17. (Currently Amended) A method according to ~~Claims 1 or 2~~Claim 1 wherein in Step 2B, the Mitsunobu reaction is conducted in the presence of a phthalimide selected from the group consisting of: phthalimide, succinimide, 4,5-dichlorophthalimide, and 1,8-naphthalimide, triphenylphosphine and diisopropylazodicarbonylate (DIAD) in an aprotic solvent selected from the group consisting of: toluene, tetrahydrofuran, ethyl acetate, and methylene chloride.

18. (Original) A method according to Claim 17 wherein the phthalimide is phthalimide, and the aprotic solvent is ethyl acetate and the reaction temperature is 20-30 °C.

19. (Currently Amended) A method according to ~~Claims 1 or 2~~Claim 1 wherein in Step 5 the addition of the sulfonamide fragment 1-5 and the epoxide fragment 2-3 occurs in the presence of a catalytic or stoichiometric amount of a moderately strong amine or phosphazene base and in an alcoholic solvent, wherein the moderately strong amine or phosphazene base is selected from the group consisting of: 1,8-diazabicyclo[5,4,0]-undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,3,4,6,7,8-hexahydro-*2H*-pyrimido[1,2-a]pyrimidine (TBD), 1,3,4,6,7,8-hexahydro-1-methyl-*2H*-pyrimido[1,2-a]pyrimidine (MTBD), tert-butylimino-tri(pyrrolidino)phosphorane (BTPP), 1-tert-butyl-2,2,4,4,4-pentakis(dimethylamino)-2λ^5, 4λ^5-catenadi(phosphazene) (P2-t-Bu), tert-butylimino-tris(dimethylamino)phosphorane (P1-t-Bu), 1-tert-butyl-4,4,4-tris(dimethylamino)-2,2-bis[tris(dimethylamino)-phosphoranylidenamino]-2λ^5, 4λ^5-catenadi(phosphazene) (P4-t-Bu), 1-ethyl-2,2,4,4,4-pentakis(dimethylamino)-2λ^5, 4λ^5-catenadi(phosphazene) (P2-Et), and the alcoholic solvent is selected from the group consisting of: isopropanol, ethanol, 2-butanol, 2-pentanol, ethylene glycol, glycerol, and tert-butyl alcohol.

20. (Original) A method according to Claim 19 wherein the moderately strong phosphazene base is tert-butylimino-tri(pyrrolidino)phosphorane (BTPP) and the alcoholic solvent is isopropanol which is at reflux.

21. (Currently Amended) A method according to ~~Claims 1 or 2~~Claim 1 wherein in Step 6 the reaction occurs in the presence of an aprotic solvent, wherein the aprotic solvent is selected from the group consisting of: 1,2 dichloroethane, methylene chloride, toluene, and tetrahydrofuran (THF) and the transition metal alkylidene catalysts are selected from a group consisting of: 1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene) ruthenium (o-isopropoxy-phenylmethylene) dichloride, tricyclohexylphosphine [1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydro-imidazol-2-ylidene][benzylidene]ruthenium (IV) dichloride, bis(tricyclohexylphosphine) benzylidene ruthenium (IV) dichloride, 2,6-diisopropylphenyl-imidoneophylidene molybdenum (VI) bis(hexafluoro-t-butoxide).

22. (Original) A method according to Claim 21 wherein the aprotic solvent is toluene which is heated to 110°C and the transition metal alkylidene catalysts is 1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene) ruthenium (o-isopropoxy-phenylmethylene) dichloride.

23. (Currently Amended) A method according to ~~Claims 1 or 2~~Claim 1 wherein in Step 7 the hydrogenation occurs at a hydrogen pressure of 80-150 psi ; the hydrogenation catalyst is a palladium on carbon catalyst selected from the group consisting of: 10% Pd/1625C (wet), 5% Pd/1625C (wet), 10% Pd/2020C (wet), 10% Pd/2055C (wet), and 10% Pd/3310C (wet) and the hydrogenation occurs in a solvent selected from the group consisting of: THF and methanol.

24. (Original) A method according to Claim 23 wherein the hydrogen pressure is 120 psi, and wherein the PMC catalyst is 10% Pd/1625C (wet) and the solvent is THF.

25. (Original) A method according to Claim 24 wherein the THF is heated at 50°C.

26. (Currently Amended) A method according to ~~Claims 1 or 2~~Claim 1 wherein Step 8 occurs in the presence of a second amine-substituted compound selected from the group consisting of: methylamine, diaminoethane, and hydrazine monohydrate and wherein Step 8 occurs in an alcoholic solvent selected from the group consisting of: methanol or ethanol.

27. (Original) A method according to Claim 26 wherein the second amine-substituted compound is hydrazine monohydrate and wherein the alcoholic solvent is ethanol.

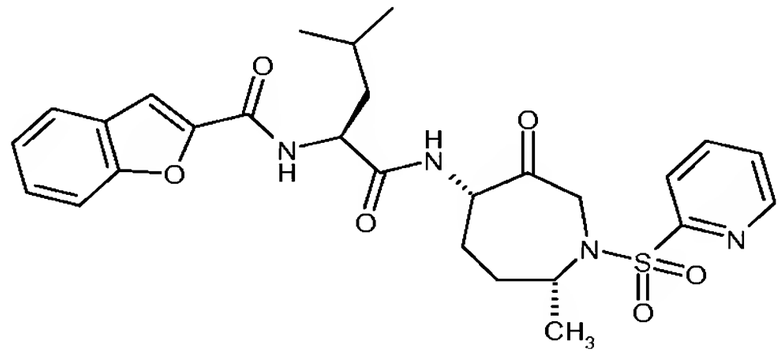
28. (Original) A method according to Claim 27 wherein the ethanol is heated at 60°C.

29. (Original) A method according to Claim 1 wherein in Step 9A the coupling of the amino alcohol 3-4 with the side chain carboxylic acid 3-5 occurs in a mixture of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC or EDC-HCl) and 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (HOOBt) in methylene chloride at 0-5°C.

30. (Original) A method according to Claim 1 wherein in Step 10A the oxidation of azepine alcohol 3-6 to provide the compound of Formula I occurs in the presence of acetic anhydride in dimethyl sulfoxide.

31. (Original) A method according to Claim 30 wherein the dimethyl sulfoxide is heated at 30-35°C.

32. (Original) A method of preparation of benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide, of Formula I:

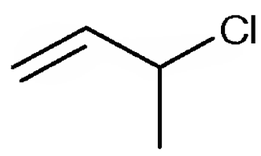


I

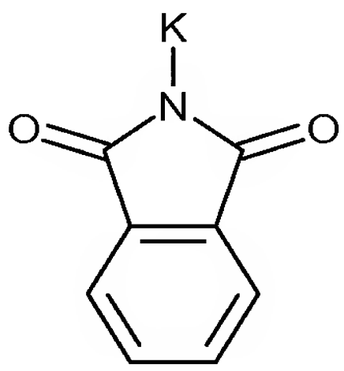
comprising the steps of:

A. preparation of a sulfonamide fragment, further comprising the steps of:

Step 1. reacting 3-chloro-1-butene 1-1 with potassium phthalimide

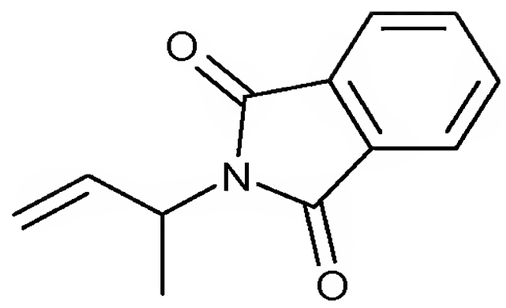


1-1



and

in DMF at 135°C in the presence of potassium carbonate to form compound 1-2, N-(α-methylallyl) phthalimide as a racemate;



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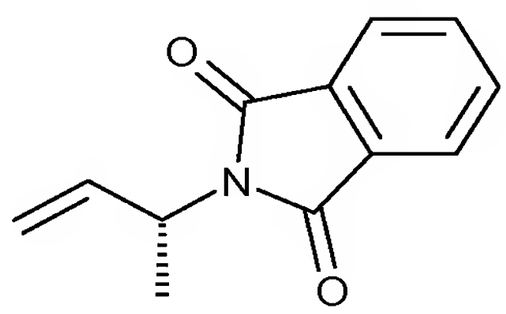
1-2

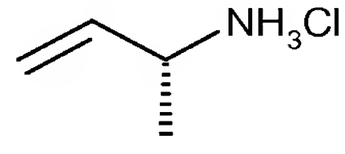
Step 2. Multiple column chromatography of racemic compound 1-2 using CHIRALPAK AD as the chiral stationary phase, and ethanol as the mobile phase, to provide the (R)-enantiomer 1-3 in at least 90% enantiomeric excess



.

1-3

Step 3. reacting compound 1-3 with ethanolamine in ethanol to form a reaction product, 2-amino-3-butene, and then purifying the reaction product by azeotropic distillation with ethanol, and then treating the purified reaction product with gaseous HCl to provide the amine hydrochloride 1-4 2-amino-3-butene hydrochloride



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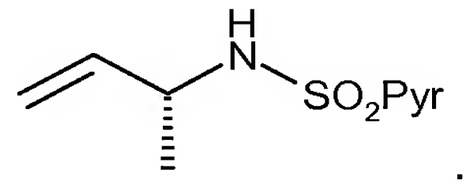
1-4

Step 4. Coupling 2-chlorosulfonyl pyridine, in methylene chloride and in the presence of TEA at 25°C, with the amine hydrochloride 1-4 to form the pyridine sulfonamide fragment 1-5, (R)-2-pyridinesulfonyl-N-(α-methylallyl) amine



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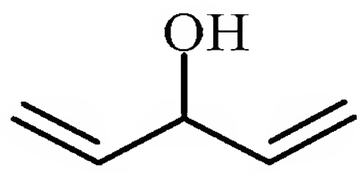
1-5

B. preparation of an epoxide fragment, further comprising the steps of:

Step 1B. epoxidation of 1,4-pentadien-3-ol 2-1 in the presence of cumene hydroperoxide, $Ti(O\textit{i}Pr)_4$ and (-)-DIPT over 4Å molecular sieves in methylene chloride at –30°C



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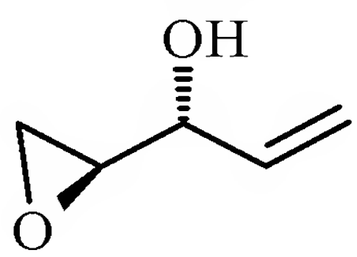
2-1

to provide (2S,3R)-1,2-epoxy-4-penten-3-ol 2-2



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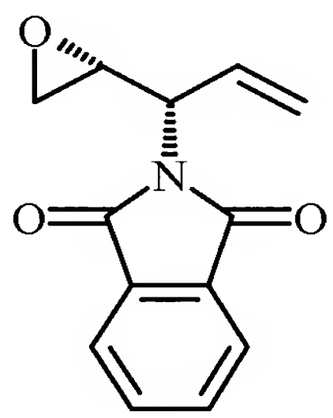
2-2

Step 2B. Mitsunobu reaction of the compound 2-2 in the presence of phthalimide, triphenylphosphine and DIAD in toluene at 20-30°C to form the nitrogen protected epoxide fragment 2-3, 2-[(1S)-1-(2R)-oxiranyl-2-propenyl]-1H-isoindole-1,3(2H)-dione

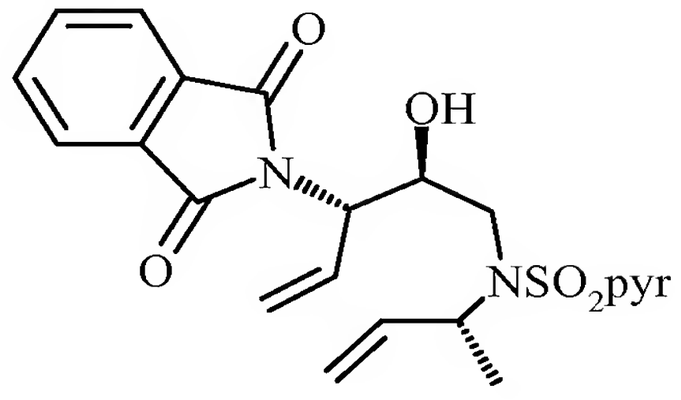


;

2-3

C. coupling of the the sulfonamide fragment and the epoxide fragment to provide the compound of Formula I, further comprising the steps of:

Step 5. addition of the sulfonamide fragment 1-5 and the epoxide fragment 2-3 in refluxing isopropyl alcohol in the presence of tert-butylimino-tri(pyrrolidino)phosphorane (BTPP) to provide *N*-[(2S,3S)-3-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)-2-hydroxy-4-pentenyl]-*N*-[(1*R*)-1-methyl-2-propenyl]-2-pyridinesulfonamide 3-1



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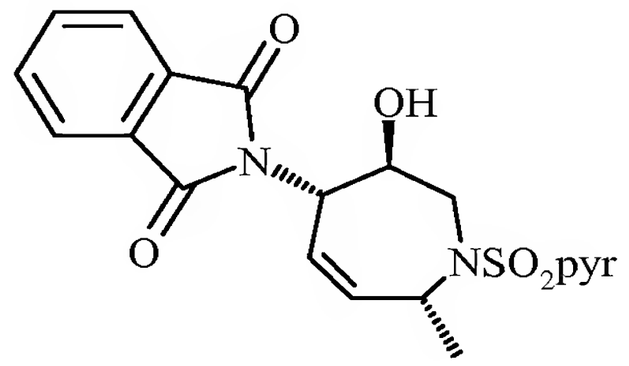
3-1

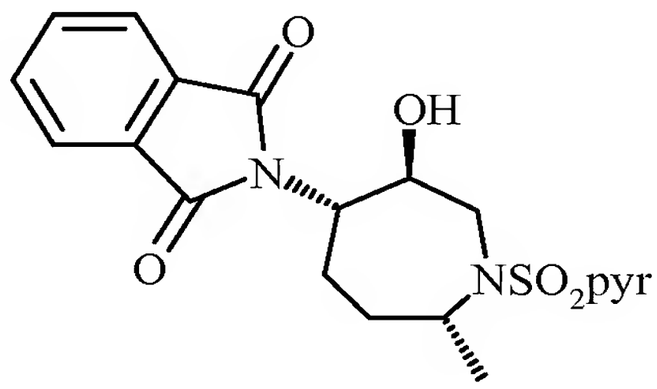
Step 6. reaction of the compound 3-1 with 1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene) ruthenium (o-isopropoxy-phenylmethylene) dichloride in toluene at 110°C to provide the compound 3-2, (3*S*,4*S*,7*R*)-4-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)-2,3,4,7-tetrahydro-7-methyl-1-(2-pyridinylsulfonyl)-1*H*-azepin-3-ol



;

3-2

Step 7. catalytic hydrogenation of the compound 3-2 with a hydrogen pressure of 120 psi over PMC 10% Pd/1625C (wet) in THF at 50°C to provide the dihydro compound 3-3, (3*S*,4*S*,7*R*)-4-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)-2,3,4,5,6,7-hexahydro-7-methyl-1-(2-pyridinylsulfonyl)-1*H*-azepin-3-ol

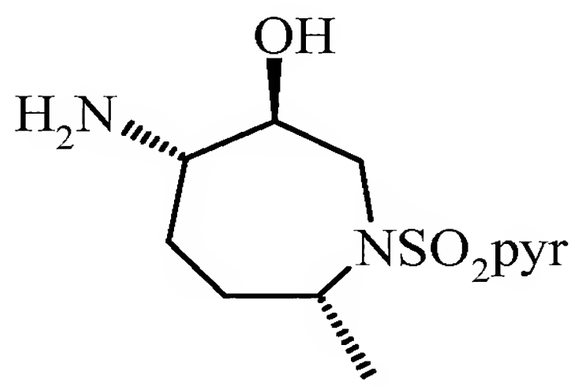


;

3-3

Step 8. deprotection of the azepanone 4-amino function of the compound 3-3 in the presence of hydrazine monohydrate in ethanol at 60 °C to provide the amino

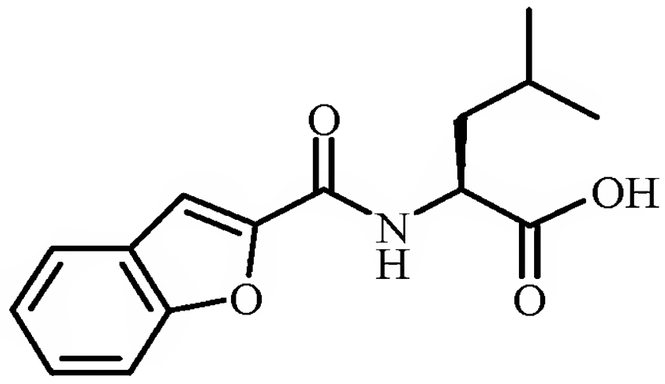
alcohol compound 3-4, (3*S*,4*S*,7*R*)-4-amino-2,3,4,5,6,7-hexahydro-7-methyl-(2-



pyridinylsulfonyl)-1*H*-azepin-3-ol ;

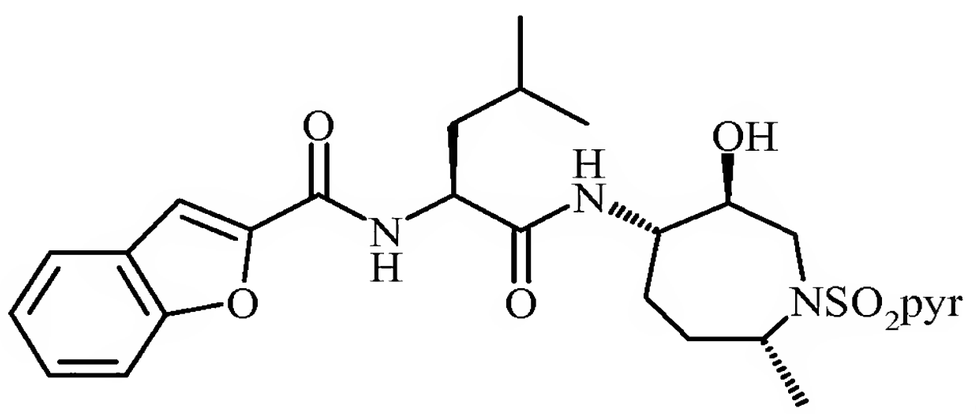
3-4

Step 9A. coupling of the amino alcohol 3-4 with the side chain carboxylic acid 3-5 in a mixture of EDC and HOOBt in methylene chloride at 0-5°C



3-5

to provide the azepine alcohol 3-6 {(S)-1-[(3S,4S,7R)-3-hydroxy-7-methyl-1-1(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide



3-6

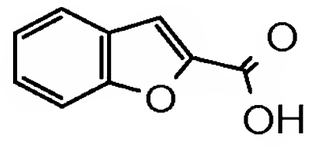
and

Step 10A. oxidation of amino alcohol 3-6 in the presence of acetic anhydride in DMSO at 30-35°C to provide the compound of Formula I.

33. (Currently Amended) A method according to ~~either Claim 1 or~~ Claim 32 wherein the 2-chlorosulfonyl pyridine used in Step 4 is prepared before Step 4 by reacting 2-mercaptopyridine, chlorine gas, and conc. HCl.

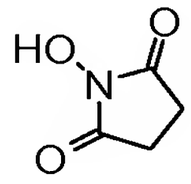
34. (Currently Amended) A method for preparing the side chain carboxylic acid 3-5 used in Step 9A of ~~Claim 1 or 32~~ Claim 1, comprising the following steps:

Step 1. esterification of benzofuran-2-carboxylic acid 4-1



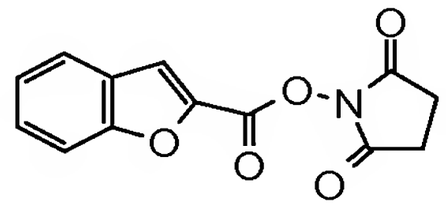
4-1

with N-hydroxysuccinimide 4-2



4-2

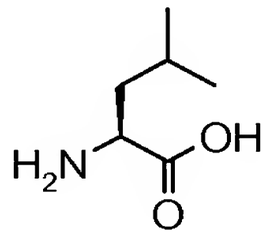
to provide the succinate ester 4-3



4-3

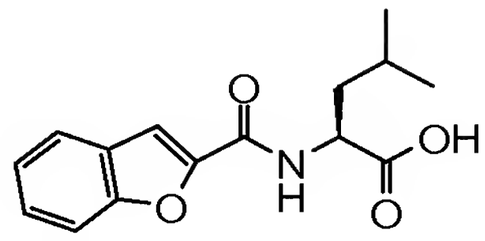
and

Step 2. amidation of succinate ester 4-3 with (*L*)-leucine 4-4



4-4

to provide the side chain carboxylic acid 3-5

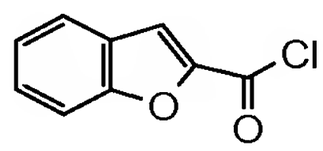


3-5.

35. (Original) A method according to Claim 35 wherein Step 1 is conducted in the presence of EDC·HCl and Step 2 is conducted in the presence of CF_3C (=NTMS)OTMS in DMF at room temperature.

36. (Currently Amended) A method according for preparing the side chain carboxylic acid 3-5 used in Step 9A of ~~Claims 1 and 32~~ Claim 1 comprising the following steps:

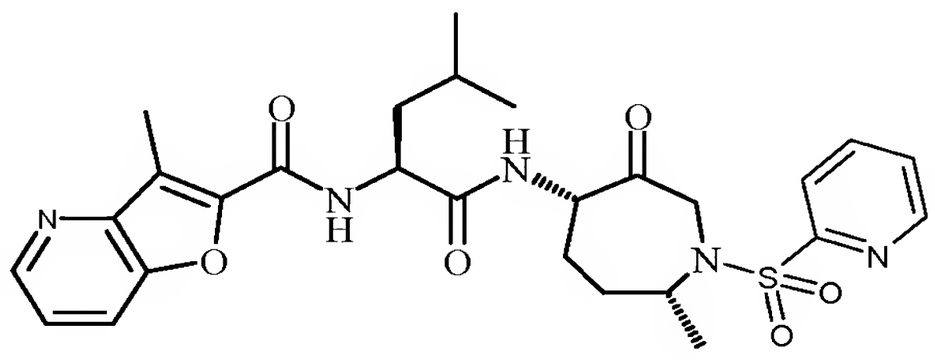
Step 1. amidation of benzofuran-2-carbonyl chloride 4-5 with (*L*)-leucine 4-4



4-5

37. (Original) A method according to Claim 36 wherein Step 1 is conducted in the presence of NaOH and K_2CO_3 in THF at 10-15 °C.

38. (Original) A method of preparation of 3-methyl-N-[(1S)-3-methyl-1-({[(4S,7R)-7-methyl-3-oxo-1-(2-pyridinylsulfonyl) hexahydro-1H-azepin-4-yl]amino}carbonyl)butyl]furo[3,2-b]pyridine-2-carboxamide, of Formula II:

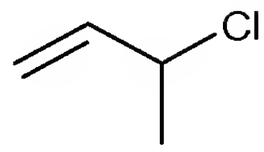


II

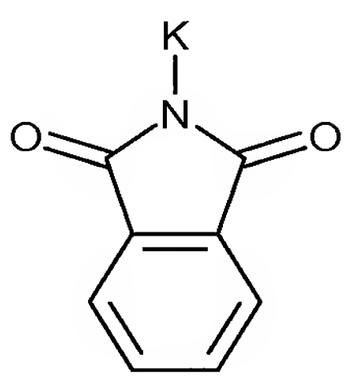
comprising the steps of:

A. preparation of a sulfonamide fragment, further comprising the steps of:

Step 1. Reacting 3-chloro-1-butene 1-1 with potassium phthalimide

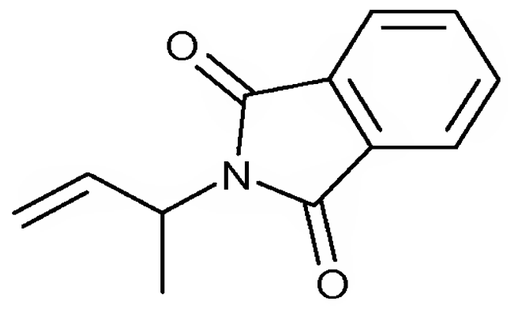


1-1



and

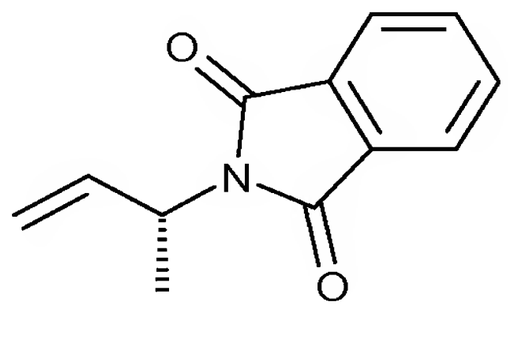
in DMF at 135°C in the presence of potassium carbonate to form compound 1-2, N-(α-methylallyl) phthalimide as a racemate;



;

1-2

Step 2. Multiple column chromatography of racemic compound 1-2 using CHIRALPAK AD as the chiral stationary phase, and ethanol as the mobile phase, to provide the (R)-enantiomer 1-3 in at least 90% enantiomeric excess



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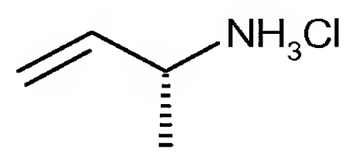
1-3

Step 3. Reacting compound 1-3 with ethanolamine in ethanol to form a reaction product, 2-amino-3-butene, and then purifying the reaction product by azeotropic distillation with ethanol, and then treating the purified reaction product with gaseous HCl to provide the amine hydrochloride 1-4 2-amino-3-butene hydrochloride



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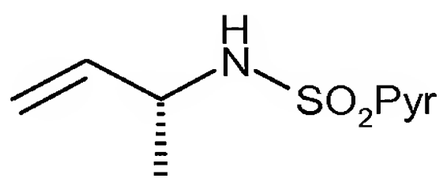
1-4

Step 4. Coupling 2-chlorosulfonyl pyridine, in methylene chloride and in the presence of TEA at 25°C, with the amine hydrochloride 1-4 to form the pyridine sulfonamide fragment 1-5, (R)-2-pyridinesulfonyl-N-(α-methylallyl) amine



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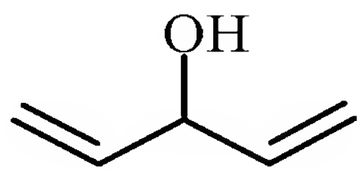
1-5

B. preparation of an epoxide fragment, further comprising the steps of:

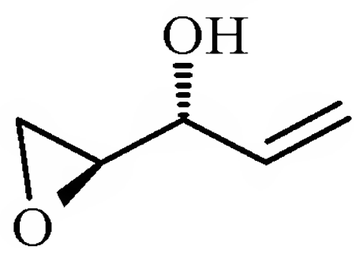
Step 1B. Epoxidation of 1,4-pentadien-3-ol 2-1 in the presence of cumene hydroperoxide, Ti(O*i*Pr)$_4$ and (-)-DIPT over 4Å molecular sieves in methylene chloride at –30°C



;

2-1

to provide (2S,3R)-1,2-epoxy-4-penten-3-ol 2-2



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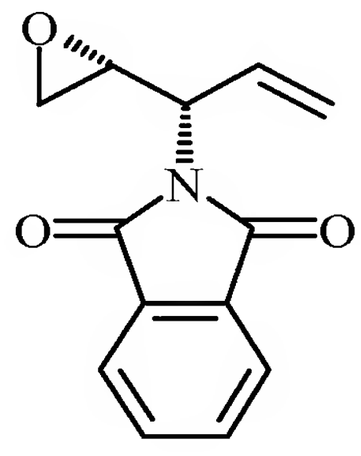
2-2

Step 2B. Mitsunobu reaction of the compound 2-2 in the presence of phthalimide, triphenylphosphine and DIAD in toluene at 20-30°C to form the nitrogen protected epoxide fragment 2-3, 2-[(1S)-1-(2R)-oxiranyl-2-propenyl]-1H-isoindole-1,3(2H)-dione

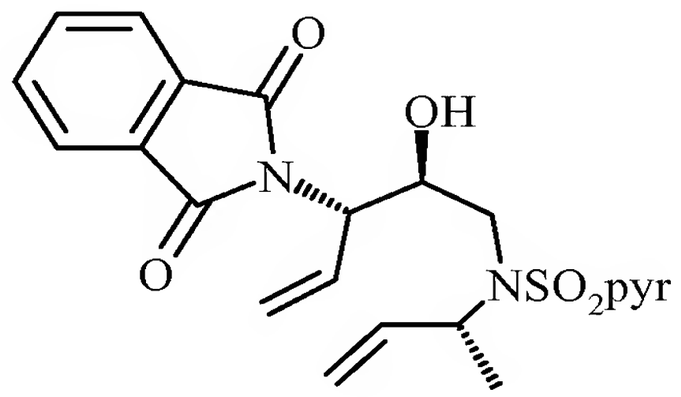


;

2-3

C. coupling of the the sulfonamide fragment and the epoxide fragment to provide the compound of Formula I, further comprising the steps of:

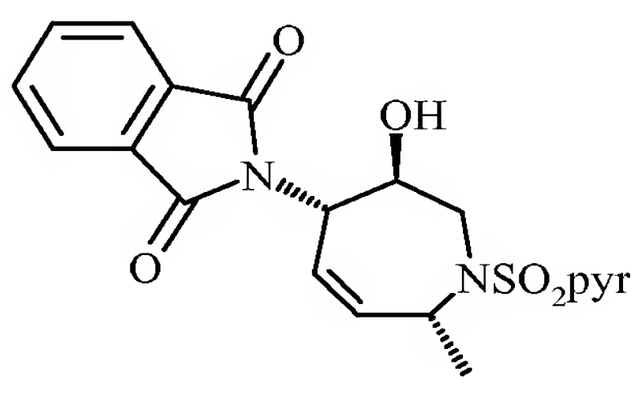
Step 5. Addition of the sulfonamide fragment 1-5 and the epoxide fragment 2-3 in refluxing isopropyl alcohol in the presence of tert-butylimino-tri(pyrrolidino)phosphorane (BTPP) to provide *N*-[(2S,3S)-3-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)-2-hydroxy-4-pentenyl]-*N*-[(1*R*)-1-methyl-2-propenyl]-2-pyridinesulfonamide 3-1



;

3-1

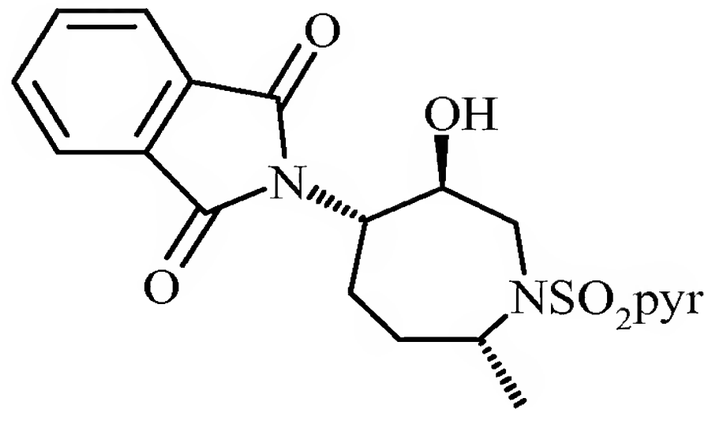
Step 6. Reaction of the compound 3-1 with 1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene) ruthenium (o-isopropoxy-phenylmethylene) dichloride in toluene at 110°C to provide the compound 3-2, (3*S*,4*S*,7*R*)-4-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)-2,3,4,7-tetrahydro-7-methyl-1-(2-pyridinylsulfonyl)-1*H*-azepin-3-ol



;

3-2

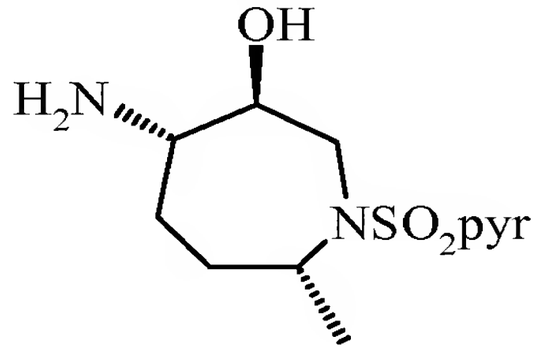
Step 7. Catalytic hydrogenation of the compound 3-2 with a hydrogen pressure of 120 psi over PMC 10% Pd/1625C (wet) in THF at 50°C to provide the dihydro compound 3-3, (3*S*,4*S*,7*R*)-4-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)-2,3,4,5,6,7-hexahydro-7-methyl-1-(2-pyridinylsulfonyl)-1*H*-azepin-3-ol



;

3-3

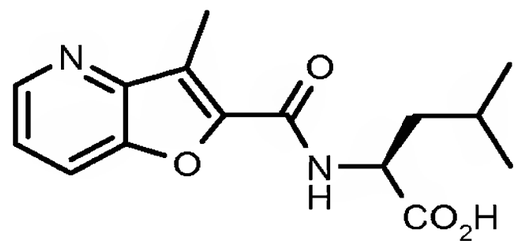
Step 8. Deprotection of the azepanone 4-amino function of the compound 3-3 in the presence of hydrazine monohydrate in ethanol at 60 °C to provide the amino alcohol compound 3-4, (3*S*,4*S*,7*R*)-4-amino-2,3,4,5,6,7-hexahydro-7-methyl-(2-



pyridinylsulfonyl)-1*H*-azepin-3-ol ;

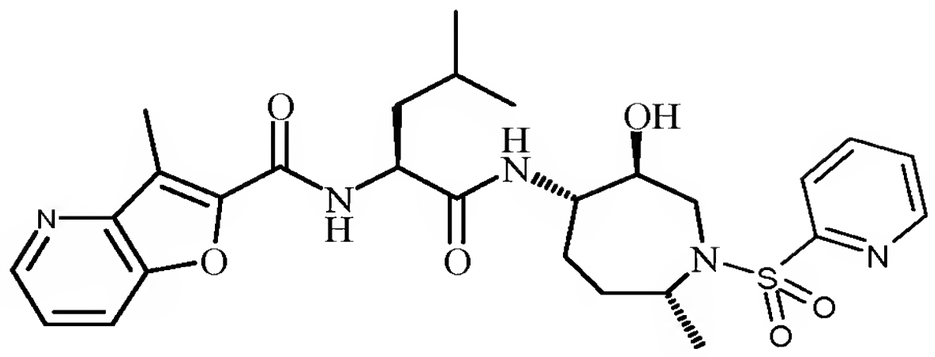
3-4

Step 9B: Coupling of the amino alcohol 3-4 with the side chain carboxylic acid 6-3 in a mixture of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC or EDC·HCl), 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (HOOBt), and N-methylmorphloline (NMM) in methylene chloride at 0-5 °C



6-3

to provide the azepine alcohol 5-1 N-[(1S)-1-({[(3S,4S,7R)-3-hydroxy-7-methyl-1-(2-pyridinylsulfonyl)hexahydro-1H-azepin-4-yl]amino}carbonyl)-3-methylbutyl]-3-methylfuro[3,2-b]pyridine-2-carboxamide;



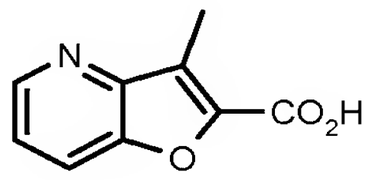
5-1

and

Step 10B, oxidation of azepine alcohol 5-1 in the presence of acetic anhydride in dimethyl sulfoxide at 30-35 °C to provide the compound of Formula II.

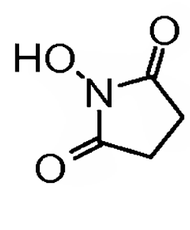
39. (Currently Amended) A method according to ~~either Claim 2 or 38~~ Claim 38 for preparing the side chain carboxylic acid 6-3 used in step 9B, comprising the following steps:

Step 1, Esterification of 3-methylfuro[3,2-b]pyridine-2-carboxylic acid 6-1



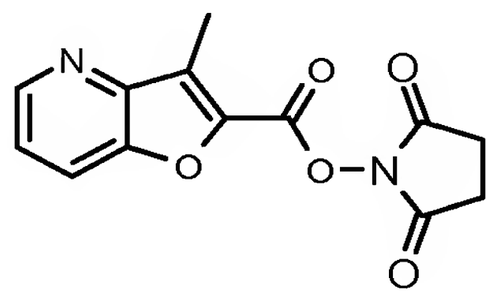
6-1

with N-hydroxysuccinimide 4-2



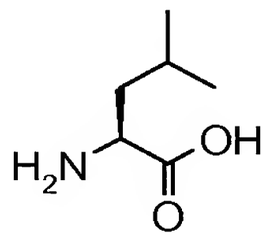
4-2

to provide the succinate ester 6-2 ;

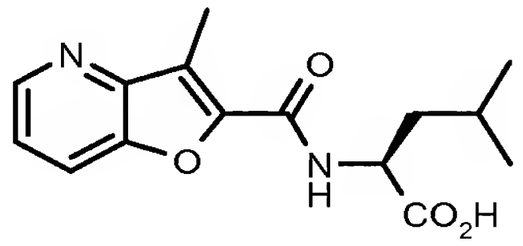


and

Step 2: Amidation of succinate ester 6-2 with (*L*)-leucine 4-4



to provide the side chain carboxylic acid 6-3

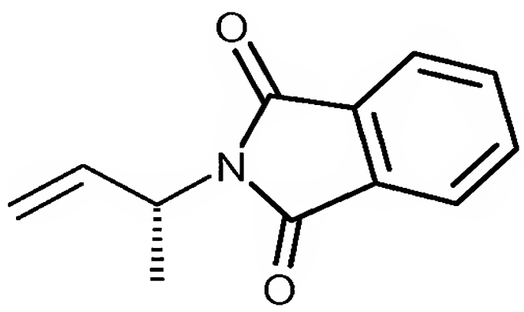


6-3.

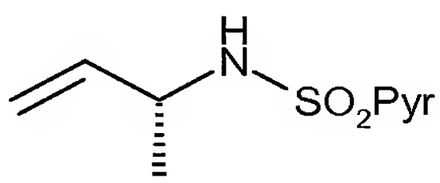
40. (Original) A method according to claim 39 wherein step 1 is conducted in the presence of EDC·DMF.

41. (Original) A method according to claim 39 wherein step 2 is conducted in the presence of ET_3N in 10% aqueous ethanol at 5 – 10 °C.

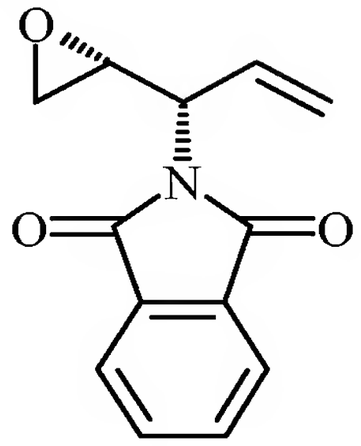
42. (Original) A compound selected from the group consisting of:



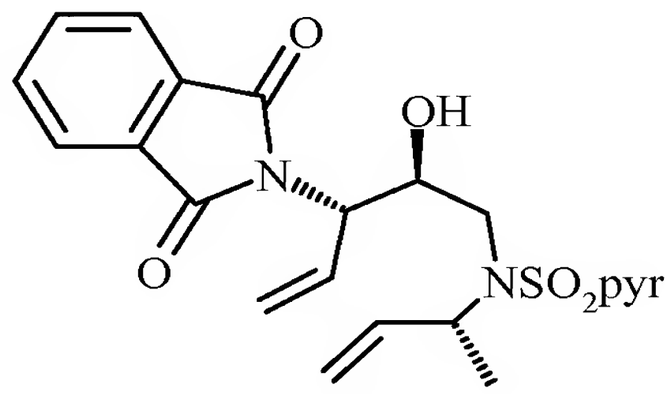
(R)-N-(α-methylallyl) phthalimide;



(R)-2-pyridinesulfonyl-N-(□ -methylallyl) amine;

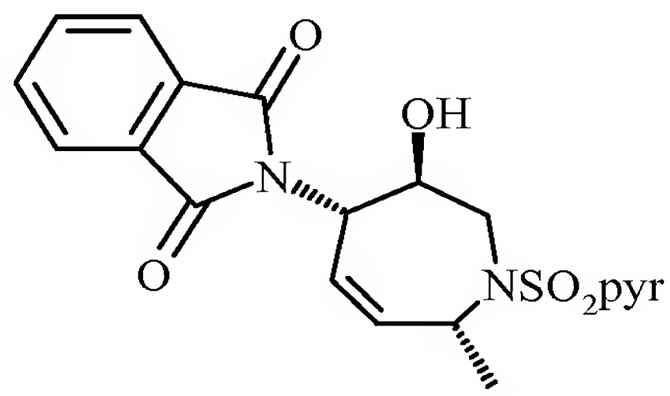


2-[(1S)-1-(2R)-oxiranyl-2-propenyl]-1H-isoindole-1,3(2H)-dione;

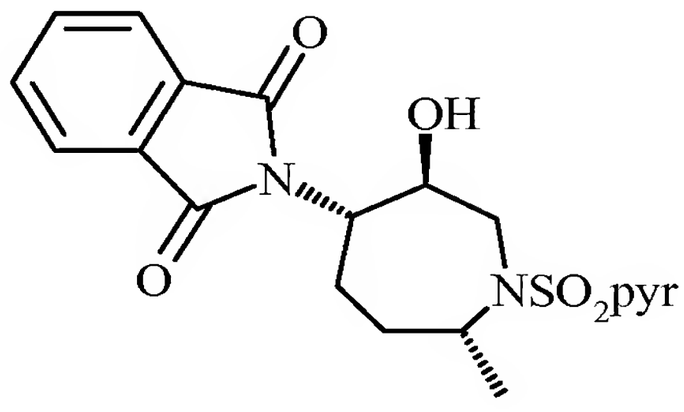


43. (Original) A compound selected from the group consisting of:

N-[(2S,3S)-3-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)-2-hydroxy-4-pentenyl]-*N*-[(1*R*)-1-methyl-2-propenyl]-2-pyridinesulfonamide;

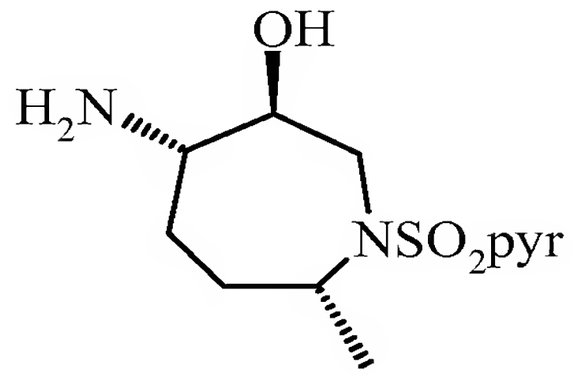


(3*S*,4*S*,7*R*)-4-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)-2,3,4,7-tetrahydro-7-methyl-1-(2-pyridinylsulfonyl)-1*H*-azepin-3-ol;

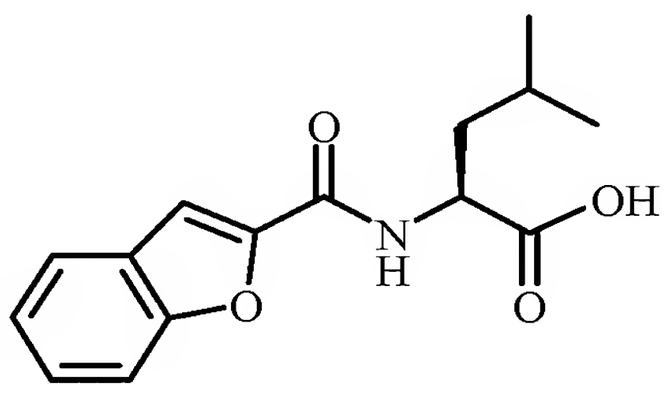


(3*S*,4*S*,7*R*)-4-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)-2,3,4,5,6,7-hexahydro-7-methyl-1-(2-pyridinylsulfonyl)-1*H*-azepin-3-ol;

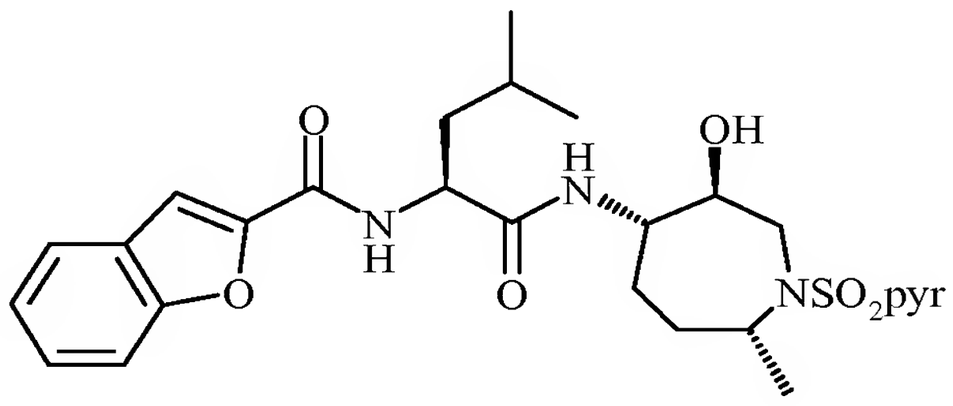
44. (Original) A compound selected from the group consisting of:



(3*S*,4*S*,7*R*)-4-amino-2,3,4,5,6,7-hexahydro-7-methyl-(2-pyridinylsulfonyl)-1*H*-azepin-3-ol;



(2*S*)-2-[(2-benzofuranylcarbonyl)amino]-4-methylpentanoic acid; and



{(S)-1-[(3S,4S,7R)-3-hydroxy-7-methyl-1-1(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide.